Abstract DOP27

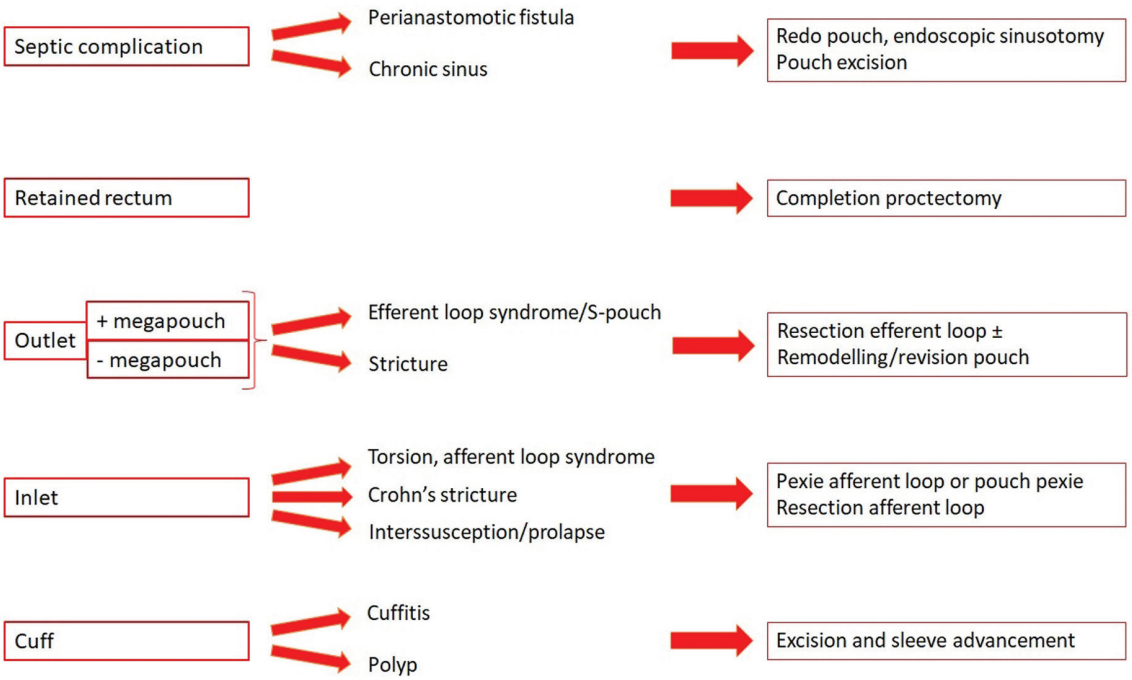


Figure 1. Surgical related pouch failure: subclassification

Background: Many different pouch failure (PF) indications and procedures are known. In literature, different types of PF are randomly classified and often stacked together due to complexity. Transanal minimally invasive surgery (TAMIS) is becoming increasingly popular for redo-surgery due to greater accessibility and visibility in complex pelvic surgery compared with the conventional abdominal approach. We aimed to evaluate the efficacy of TAMIS in patients with PF.

Methods: This retrospective study includes all consecutive patients over 18-year old with an ileal pouch-anal anastomosis (IPAA) and PF that were managed with TAMIS between July 2014 and July 2019. Patient characteristics, operative indications, perioperative outcomes and short-term follow-up (FU) are described using a suggested subclassification for surgical-related PF (Figure 1).

Results: Forty-six procedures were completed in 42 patients, predominantly male (66.7%) with a median age of 44.6 (range 22.0–70.8) years. Initial IPAA indications were familial adenomatous polyposis (n = 11), medical refractory ulcerative colitis (UC) (n = 29) or other (n = 2). Seven (24.1%) UC patients turned out to have Crohn's disease (CD). Reasons for PF were septic complications (n = 18), retained rectum (n = 3), outlet problems (n = 8) (with megapouch: n = 5), inlet problems (n = 6), cuff problems (n = 8) and refractory pouchitis with unknown aetiology (n = 3). Twenty-three pouch redo's (16 remodelling, 7 new pouches), 5 sleeve advancements, 4 cuff excisions, 1 posterior pouchpexy, and 13 pouch excisions were recorded. Five pouch excisions were performed in CD patients. Five procedures were fully completed transanally, and 41 were a combined transabdominal (with 32 open and 9 laparoscopic) and TAMIS approach. None were converted to an open procedure. Apart from the patients with a pouch excision, 9 ended up with a permanent ileostomy, although technical success was achieved in 4 of those. Six permanent ileostomies were in patients with a redo-pouch (3 remodelling, 3 new pouches), 2 after sleeve advancement and 1 after cuff excision. Major morbidity (Clavien-Dindo ≥3) occurred after 17 procedures (37.0%), 14 within 1 month after surgery with a median FU of 17.9 (0.9–41.6) months. There was no peri-operative mortality.

Conclusion: TAMIS for PF after IPAA is technically feasible with acceptable short-term outcomes. Peri-operative morbidity is high and reflects the complexity of these procedures. Success after PF procedures is difficult to interpret due to a wide range of possible outcomes such as technical success, conversion rate and number of patients with a permanent stoma. The PF subclassification makes the complex problem and surgical management of PF comprehensible.

DOP Session 4 - From the bench to the crystal ball: Predicting outcomes with novel markers

DOP28

Understanding the molecular mechanisms of anti-TNF treatment failure in patients with Crohn's disease: A pilot serum proteomic analysis of the PANTS cohort

S. Lin*[1,2], N. Chanchlani[1,2], B.M. Invergo[3], M.W. Anderson[3], H.M. Guay[4], M. Reppell[4], J.W. Butler[4], J.R. Goodhand[1,2], T. Ahmad[1,2], N.A. Kennedy[1,2], Exeter IBD Pharmacogenetics Research Group

[1]*Exeter IBD Pharmacogenetics Research Group, University of Exeter, Exeter, UK,* [2]*Department of Gastroenterology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK,* [3]*Translational Exchange @ Exeter- Living Systems Institute, University of Exeter, Exeter, UK,* [4]*Department of Research and Development, AbbVie Inc., North Chicago, USA*

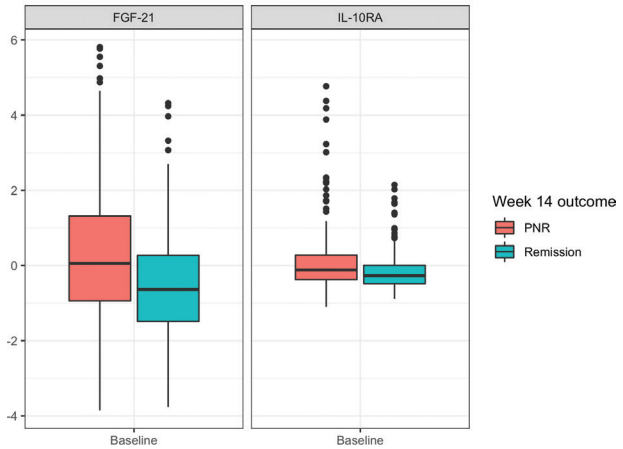
Background: Proteomic biomarkers have been linked to anti-TNF treatment failure, but previous studies have been insufficiently powered to stratify associations by drug level. The Personalised Anti-TNF

Therapy in Crohn's disease (PANTS) is a prospective UK-wide study investigating treatment failure in 1610 anti-TNF naïve patients. We aimed to identify proteomic markers of treatment failure.

Methods: We sampled patients with primary non-response (PNR) (n = 223) and remission (n = 219) who had a baseline CRP ≥4 mg/l and/or calprotectin >100 µg/g. PNR was defined at week 14 as ongoing steroids, or both of HBI failed to fall by ≥3 points or to ≤4 and CRP failed to fall by ≥50% or to ≤3 mg/l. Non-remission at week 54 was defined as HBI >4 and CRP >3 mg/l and no steroids. Targeted serum proteomic analysis of 180 proteins using Olink Inflammation and Immune Response panels were performed. Mann–Whitney U tests were used to identify baseline proteins that predicted PNR and non-remission. Sub-group analyses stratified by drug level were undertaken. Pharmacokinetic (PK) failure was defined as PNR with low drug level (infliximab level <2 mg/l, adalimumab level <6 mg/l) and pharmacodynamic (PD) failure as PNR despite adequate drug level. Significant proteins were entered into multivariable logistic regression models and Bayesian information criterion (BIC) with backward stepwise selection were used to build predictive models of treatment failure. We applied 10-fold cross-validation to test the models. P-values of < 0.05 were considered significant.

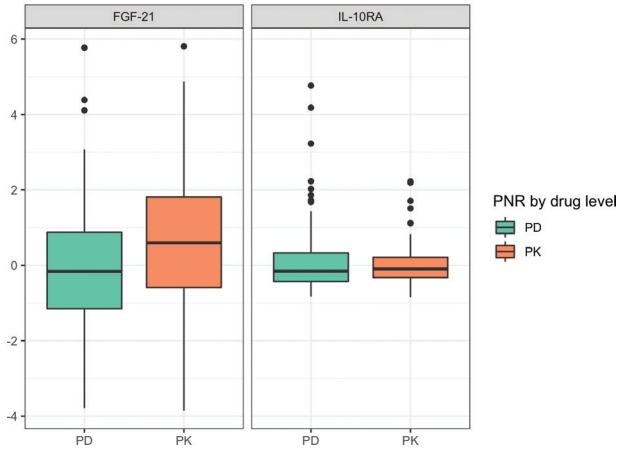
Results: Elevated fibroblast growth factor 21 (FGF21) (OR 1.3, CI 1.1–1.4, $p = 3.4 \times 10^{-5}$) and interleukin-10 receptor subunit α (IL10RA) (OR 1.6, CI 1.2–2.1, $p = 6.3 \times 10^{-4}$) predicted PNR (Figure 1). At week 14, FGF21 (OR 1.5, CI 1.3–1.9, $p = 1.8 \times 10^{-6}$) and IL10RA (OR 1.8, CI 1.3–2.3, $p = 5.8 \times 10^{-5}$) levels were also associated with PNR.

Figure 1: Baseline significant proteins to week 14 outcome



Sub-group analyses showed baseline FGF21 (OR 1.4, CI 1.2–1.7, $p = 2.0 \times 10^{-4}$) predicted PK failure and that IL10-RA (OR 1.6, CI 1.1–2.2, $p = 6.7 \times 10^{-3}$) predicted PD failure (Figure 2).

Figure 2: Baseline significant proteins to PNR stratified by drug level



In separate models, non-remission at week 54 was predicted by baseline (FGF21; OR 1.3, CI 1.1–1.4, $p = 1.4 \times 10^{-4}$, IL10-RA; OR 1.5, CI 1.1–2.0, $p = 3.6 \times 10^{-3}$) and week 14 (FGF21; OR 1.4, CI 1.2–1.7, $p = 3.6 \times 10^{-4}$, IL10-RA; OR 1.7, CI 1.3–2.4, $p = 1.7 \times 10^{-4}$) FGF21 and IL10-RA levels. Model validation of baseline FGF21 and IL10-RA showed an area under the curve of 0.61 (CI 0.57–0.64) for PNR and 0.60 (CI 0.56–0.64) for non-remission at week 54.

Conclusion: Our study identified FGF-21 and IL10-RA as proteins of interest associated with PK and PD treatment failure, respectively. Functional studies to determine the molecular mechanism driving dysregulation of these proteins are required.

DOP29

Elevation of a novel blood-based gene signature in a severe Crohn's disease (CD) subtype preceding surgery defines and predicts a post-surgical decrease in pro-inflammatory pathway activation

R. Gonsky*[1], P. Fleshner[2], G. Botwin[1], E. Biener-Ramanujan[1], D. McGovern[1], S. Targan[1]

[1]*Cedars Sinai Medical Center, Inflammatory Bowel and Immunobiology Research Institute, Los Angeles, California, USA,* [2]*Cedars Sinai Medical Center, Department of Surgery, Los Angeles, CA, USA*

Background: CD is defined by transmural inflammation leading to inflammatory, stricturing and/or penetrating phenotypes. Identifying underlying molecular pathways and distinct disease subsets is critical for improved prognostics, therapeutics and biomarker discovery.

Methods: $CD3^+$ T cells were purified from paired blood and mucosal tissue from 101 CD and 17 non-IBD subjects requiring surgery. Longitudinal samples (n = 30) were collected 4–13 mo. post-surgery. Expression profiles were generated by RNAseq, T-cell subset deconvolution by xCell and transcriptome-wide associations (TWAS) using TWAS-hub.

Results: Unsupervised clustering of peripheral T-cell gene expression at surgery revealed 2 CD profiles: Expression from cluster1, labelled CD-PBT (63%), clustered tightly with the non-IBD group. In cluster2, expression shifted from a peripheral toward a mucosal profile, labelled CD-PBmu(cosal) (37%). CD-PBmu was defined by differentially expressed genes (DEG) (1944 DEG, p < 0.001) regulating cell migration and adhesion pathways and a distinct T-cell subset composition associated with stricturing disease (p = 0.03), increased resected bowel length (p = 0.036) and post-op recurrence (p = 0.01). There were no significant differences in disease location/behaviour. Independent validation (5 public datasets) confirmed the CD-PBmu signature in data from whole blood (CD patients failing anti-TNF therapy, n = 204) and the mucosal-like expression profile in data from ileal tissue (paediatric CD patients, studies n = 751). A defining feature of CD-PBmu, validated in a separate CD cohort (n = 19), was decreased pro-inflammatory cytokine/chemokine and adhesion molecule expression following surgery (900 DEG, p < 0.001). No post-surgery change in expression was detected in CD-PBT. A 44-gene classifier was identified to enable clinical application. The classifier accurately detected the CD-PBmu patient subtype, correlated with the altered composition of peripheral T-cell subsets and overlapped with IBD associated TWAS signals (>60%).